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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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09/234,606 01/21/99 WOLFF

J MIRUS.010

HM12/1102

MARK K JOHNSON
P O BOX 510644
NEW BERLIN WI 53131-0644

EXAMINER

NGUYEN, D

ART UNIT

PAPER NUMBER

1633

DATE MAILED:

11/02/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

FILE

Office Action Summary

Application No.

09/234,606

Applicant(s)

Wolff

Examiner

Dave Nguyen

Group Art Unit

1633

☒ Responsive to communication(s) filed on Aug 10, 2000☐ This action is **FINAL**.☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims☒ Claim(s) 1 and 3-13 is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.☒ Claim(s) 1 and 3-13 is/are rejected.☐ Claim(s) _____ is/are objected to.☐ Claims _____ are subject to restriction or election requirement.**Application Papers**☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.☐ The drawing(s) filed on _____ is/are objected to by the Examiner.☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.☐ The specification is objected to by the Examiner.☐ The oath or declaration is objected to by the Examiner.**Priority under 35 U.S.C. § 119**☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been
☐ received.☐ received in Application No. (Series Code/Serial Number) _____.☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).**Attachment(s)**☒ Notice of References Cited, PTO-892☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 3☐ Interview Summary, PTO-413☐ Notice of Draftsperson's Patent Drawing Review, PTO-948☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

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Claim 2 has been deleted; and claims 1, 3-5, 10, and 11 have been amended by the amendment filed on August 10, 2000.

Claims 1, and 3-13, to which the following grounds remain and/or are applicable, are pending.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 6-8, and 9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 6-8 are indefinite because the claims are dependent on a canceled base claim.

Claim 9 is indefinite in the recitation of "signal" because it is not apparent as to what is exactly the metes and bounds of the term. It is not apparent as to how the "signal" is positively linked to the delivery process, nor is it apparent as to what is exactly the structure of the "signal". Is it a compound, molecule, peptide, antibody, or liquid, or metal, or solid? The "signal" is also relative in meanings and does not clarify as to what is the intended purpose of the "signal" with respect to the preamble of the base claim. A change of "signal" to "targeting ligand", for example, would obviate the rejection.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

- (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
- (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

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(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 1, 3, and 9 are rejected under 35 U.S.C. 102(e) as being anticipated by Hansen (US Pat No. 5,851,527).

The claims encompass a process for delivery of chemical drugs, and protein polymers coding for toxins or cytokines to a cell, which process comprises associating a chelator to a polymeric carrier (polylysine or polydextran) that contains one or more polymers and an targeted antibody conjugated to a therapeutic protein polymer, and delivering the associated carrier to a cell, wherein the one or more polymers include polylysine and dextran polymers.

Hansen teach an identical delivery process as indicate above on column 11, lines 1-51, and column 13, first and second paragraphs.

Absent evidence to the contrary, the delivery process of Hansen has all of the properties cited in the claims.

In response to applicant's assertion (the response page 2 bridging page 3) that the '527 patent describes binding a substrate to its conjugate with a chelator for nuclear imaging, and that "the compound" is not delivered to the inside of a cell nor is delivery to the inside of a cell, the comments are not persuasive because while the '527 patent teaches a method of using a chelator conjugated to a polymer conjugate for monitoring the clearance rate of the polymer conjugate, the '527 patent does teach the delivery of the polymer conjugate to the inside of a target cell. For example, not only method of imaging a target site having a deposit of the polymer conjugate is taught by the '527 patent, method of employing the polymer conjugate to induce cytotoxicity in a tumor is also taught by the '527 patent (column 12, lines 15 and 15; see columns 19 and 20, issued claims). In addition, given that the material (polymer associated with a chelator and target cells including tumor cells) and the method step (any administering step known in the prior art) as recited in the claims are identical to that of the teaching provided in the '527 patent, any therapeutic protein polymer disclosed in the '527 patent would be delivered to the inside of the target cell, particularly in

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the absence of evidence to the contrary. Note that it is well recognized in the art the protein polymers including cytokines, for example, once deposited at a target site would naturally diffuse into the target cell either by passive or active diffusion process.

Claims 1, 3-5, and 9 are rejected under 35 U.S.C. 102(e) as being anticipated by Hnatowich *et al.* (US Pat No. 5,980,861).

The claims encompass a process for delivery of radiolabeled nucleic acid molecules or radiolabeled peptide nucleic acid to a cell, which process comprises associating a crown ether to either a nucleic acid polymer or a peptide nucleic acid polymer through a polyamine linker, mixing the crown ether containing nucleic acid polymer with a polymer carrier, and delivering the crown ether containing nucleic acid polymer complexed with the polymeric polymer to a cell.

Hnatowich *et al.* teach an identical delivery process as indicated above on column 2 bridging column 3; column 3 bridging column 4; column 6, last paragraph; column 9, first paragraph; column 11, lines 1 to lines 54; column 12 bridging column 13; column 19, first paragraph; and columns 43 and 44.

Absent evidence to the contrary, the delivery process cited in Hnatowich *et al.* has all of the properties cited in the claims.

In response to applicant's assertion that in the '861 patent, the polymer is used as a signal to direct the complex (chelator conjugated to a polymer) to a tumor site where the radioactive isotopes attempt to destroy the tumor, and that Applicants deliver their polymer into a cell for nondestructive activity, the comments are not persuasive because:

- With respect to the "polymer is used as a signal" only, the '861 patent clearly teaches throughout its specification that polymer including cDNA, peptide nucleic acid, antisense molecules are delivered to and into a target cell, e.g., column 6, last paragraph, column 7, especially lines 1-4, entire column 8, especially lines 29-67; column 9, first paragraph, column 4, lines 5-67. Not only that '861 patent teach complexes of nucleic acid molecules associated with a chelator, the patent on column 19 further teaches that polymeric carriers including

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polyglycolic acid can be associated or linked to the DNA-chelator complex as controlled release formulation to enhance the delivery of DNA polymer to a target cell.

- With respect to the applicant's assertion as to newly found use of the claimed invention, *e.g.*, non-destructive activity", the comments are not persuasive because such recitation is not even recited in any of the pending claims, and thus, there is no nexus between applicant's assertion and the subject matter being sought in the claims; and
- Applicants' claims only required a two component composition: a chelator associated with a polymer, wherein the composition is clearly taught by the cited prior art, and a method of using well-know delivery steps (*in vitro* and/or *in vivo*) to carry out the delivery of the composition, wherein the delivery steps are also taught by the cited prior art. Furthermore, even if the new "use" of the composition is directed to a result of that composition (which is not based on breadth of the claims and the teachings provided by the cited prior art), the claims are anticipated by any prior art that discloses identical materials and method steps as recited in the claims.

Claims 1 and 3 are rejected under 35 U.S.C. 102(a) or 102(e) or as being anticipated by Wolff *et al.* (US Pat No. 5,693,622). Claims 1 and 3 are also rejected under 35 U.S.C. 102(f) because the applicant did not invent the claimed subject matter.

The claims encompass a process for delivery polymeric macromolecules including a DNA coding for a protein polymer conjugated to a targeting ligand to a cell, which process comprises associating a chelator to the DNA.

Wolff teaches an identical delivery process as indicated above on column 4, lines 52-54, column 19, lines 37-50; column 25, lines 3-10, column 54, claim 21.

Absent evidence to the contrary, the delivery process cited in Wolff *et al.* has all of the properties cited in the claims.

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Claims 10-13 are rejected under 35 U.S.C. 102(b) as being anticipated by Pitha *et al.* (Biochimica et Biophysica Acta, 425, 287-295, 1976, IDS).

Pitha teaches a composition comprising a polynucleotide complexed with a polycrown in the presence of a salt, and a process of preparing the composition by associating the polynucleotide to the polycrown in the presence of a salt.

Absence evidence to the contrary, the composition and the process described in Pitha have all of the functional properties cited in the claims.

Claims 1, 3, and 9-13 are rejected under 35 U.S.C. 102(b) as being anticipated by Kayyem *et al.* (WO 96/11712; IDS).

Kayyem teaches a process for delivery an anionic polymer (DNA)-cationic polymer complex conjugated to a plurality of chelators bound to a contrast agent (page 8, first and second paragraphs; page 9, second paragraph, page 10, third paragraph, page 11, second paragraph, pages 12 and 13, and pages 26-32. Kayyem teaches that a plurality of chelators can be added to the -NH₂ groups of the lysine side chains as linkers for binding to a plurality of contrast agents (page 10, third paragraph), and that a chelator can be conjugated to any of the disclosed polymeric molecule (page 12). In addition, Kayyem discloses on page 26 that pharmaceutically acceptable carriers including a salt are employed in the preparation of a conjugate of chelators and a cationic polymer.

Absent evidence to the contrary, the delivery process and the compositions or conjugates disclosed in Kayyem have all of the properties cited in the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be

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patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, and 3-5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kayyem *et al.* taken with Hnatowich *et al.* (US Pat No. 5,980,861).

To the extent that Kayyem does not teach explicitly crown ether or polymers associated with a plurality of crown ether chelators, Hnatowich teaches that it is routine in the art at the time the invention was made for one of ordinary skill in the art to employ known chelators including crown ether for conjugation to a polymer either by covalent bonding or ionic bonding for purpose of real time monitoring of the delivery of polymers including DNA (entire document, especially columns 11 and 12). In addition, Hnatowich teaches that crown ether chelators can be covalently bound to the anionic polymer (DNA) through the nitrogen atom that is provided on the nucleic acid, or through other functional moieties bound to the anionic polymer (column 12).

It would have been obvious for one of ordinary skill in the art to have employed any chelator including crown ether in the conjugate or composition of Kayyem. One of ordinary skill in the art would have been motivated to have employed crown ether as a chelator for the purpose of either conjugating covalently to the anionic polymer (DNA) through the nitrogen atom that is provided on the nucleic acid, or of conjugating covalently to the -NH₂ moiety of the cationic polymer such as polylysine because Hnatowich teaches that chelator moieties of crown ether known in the prior art are effective chelators for use in real time monitoring of the delivery of polymers to cells *in vivo*, and because Kayyem *et al.* teaches that any of

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the known paramagnetic metal ion chelators can be used for the purpose of real time monitoring of the delivery of polymers including DNA to target cells *in vivo*.

Thus, the claimed invention as a whole was *prima facie* obvious.

Claims 1, 3-5, and 10-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wolff *et al.* (US Pat No. 5,693,613) taken with Kayyem, Hollister (WO 96/40274), and Hnatowich.

To the extent that Wolff *et al.* does not teach association of a polychelator to the DNA, and that the polychelator comprises a crown ether, Kayyem teaches a process for delivery an anionic polymer (DNA)-cationic polymer complex conjugated to a plurality of chelators bound to a contrast agent (page 8, first and second paragraphs; page 9, second paragraph, page 10, third paragraph, page 11, second paragraph, pages 12 and 13, and pages 26-32. Kayyem teaches that a plurality of chelators can be added to the -NH₂ groups of the lysine side chains as linkers for binding to a plurality of contrast agents (page 10, third paragraph), and that a chelator can be conjugated to any of the disclosed polymeric molecule (page 12). In addition, Kayem discloses on page 26 that pharmaceutically acceptable carriers including a salt are employed in the preparation of a conjugate of chelators and a cationic polymer. Kayem further teaches that the advantage of employing a chelator or polychelator (polylysine associated with a plurality of chelators) is to incorporate a real time monitoring of the delivery of polymers including DNA to target cells *in vivo*. In addition, Hollister teaches that by employing a polychelator (polylysine associated with a plurality of chelators) for medical imaging, the advantages would include a delivery of a plurality of diagnostically effective metal ions simultaneously, and an enhancement of an imaging contrast as a result of increased relaxivity (page 2).

In addition, Hnatowich teaches that it is routine in the art at the time the invention was made for one of ordinary skill in the art to employ known chelators including crown ether for conjugation to a polymer either by covalent bonding or ionic bonding for purpose of real time monitoring of the delivery of polymers including DNA (entire document, especially columns 11 and 12). In addition, Hnatowich teaches that crown ether chelators can be covalently bound to the anionic polymer (DNA) through the nitrogen atom that is

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provided on the nucleic acid, or through other functional moieties bound to the anionic polymer (column 12).

It would have been obvious for one of ordinary skill in the art to have associated any polychelator known in the prior art to a composition comprising a salt and a DNA of Wolff. One of ordinary skill in the art would have been motivated to have employed a polychelator to operably link to the DNA of Wolff because Kayem teaches that the advantage of employing a chelator or polychelator (polylysine associated with a plurality of chelators) is to incorporate a real time monitoring of the delivery of polymers including DNA to target cells *in vivo*, and because Hollister teaches that by employing a polychelator (polylysine associated with a plurality of chelators) for medical imaging, the advantages would include a delivery of a plurality of diagnostically effective metal ions simultaneously, and an enhancement of an imaging contrast as a result of increased relaxivity (page 2).

With respect to claims 3-5, it would also have been obvious for one of ordinary skill in the art to have employed any chelator including crown ether in the conjugate or composition of Wolff. One of ordinary skill in the art would have been motivated to have employed crown ether as a chelator for the purpose of either conjugating covalently to the anionic polymer (DNA) through the nitrogen atom that is provided on the nucleic acid, or of conjugating covalently to the -NH₂ moiety of the cationic polymer such as polylysine because Kayem teaches that any of the known paramagnetic metal ion chelators can be used for covalent bond to any DNA intended for delivery, and Hnatowich teaches that that it is routine in the art for one of ordinary skill in the art to employ known chelators including crown ether for conjugation to a polymer either by covalent bonding or ionic bonding for purpose of real time monitoring of the delivery of polymers including DNA.

Double Patenting Rejection

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

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A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 3-5, and 10-13 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim of U.S. Patent No. 5,693,613, and further in view of Kayem, Hollister (WO 96/40274), and Hnatowich. Although the conflicting claims are not identical, they are not patentably distinct from each other because.

Claim 21 of the '613 patent and claims 1 and 3 of this instant application encompass a gene delivery process of employing a DNA vector associated with a chelator to deliver the DNA to or into a target cell.

Insofar as claim 21 of Wolff *et al.* does not recite association of a polychelator to the DNA, and does not recite that the polychelator comprises a crown ether, Kayem teaches a process for delivery an anionic polymer (DNA)-cationic polymer complex conjugated to a plurality of chelators bound to a contrast agent (page 8, first and second paragraphs; page 9, second paragraph, page 10, third paragraph, page 11, second paragraph, pages 12 and 13, and pages 26-32. In addition, Kayem discloses on page 26 that pharmaceutically acceptable carriers including a salt are employed in the preparation of a conjugate of chelators and a cationic polymer. Kayem further teaches that the advantage of employing a chelator or polychelator is to incorporate a real time monitoring of the delivery of polymers including DNA to target cells *in vivo*. In addition, Hollister teaches that by employing for medical imaging, the advantages would include a delivery of a plurality of diagnostically effective metal ions simultaneously, and an enhancement of an imaging contrast as a result of increased relaxivity (page 2).

In addition, Hnatowich teaches that it is routine in the art at the time the invention was made for one of ordinary skill in the art to employ known chelators including crown ether for conjugation to a polymer

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either by covalent bonding or ionic bonding for purpose of real time monitoring of the delivery of polymers including DNA (entire document, especially columns 11 and 12). In addition, Hnatowich teaches that crown ether chelators can be covalently bound to the anionic polymer (DNA) through the nitrogen atom that is provided on the nucleic acid, or through other functional moieties bound to the anionic polymer (column 12).

It would have been obvious to one of ordinary skill in the art that the claimed invention reciting a DNA composition comprising a polychelator, a DNA plasmid vector, and a pharmaceutically acceptable carrier of salt is directed to obvious variants of the claimed invention of claim 21 as recited in the '622 patent because:

- Kayem teaches that the advantage of employing a chelator or polychelator (polylysine associated with a plurality of chelators) is to incorporate a real time monitoring of the delivery of polymers including DNA to target cells *in vivo*;
- Hollister teaches that by employing a polychelator for medical imaging, the advantages would include a delivery of a plurality of diagnostically effective metal ions simultaneously, and an enhancement of an imaging contrast as a result of increased relaxivity (page 2); and
- Kayem teaches that any of the known paramagnetic metal ion chelators can be used for covalent bond to any DNA intended for delivery, and Hnatowich teaches that that it is routine in the art for one of ordinary skill in the art to employ known chelators including crown ether for conjugation to a polymer either by covalent bonding or ionic bonding for purpose of real time monitoring of the delivery of polymers including DNA.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to *Dave Nguyen* whose telephone number is (703) 305-2024.

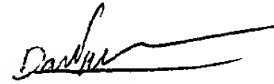
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *John LeGuyader*, may be reached at (703) 308-0447.

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Any inquiry of a general nature or relating to the status of this application should be directed to the
Group receptionist whose telephone number is (703) 308-0196.



Dave Nguyen

Patent Examiner

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